LETTERS

BRL 43694: A Novel Antiemetic to Prevent Nausea and Vomiting Induced by Chemotherapy

High-dose metoclopramide has been widely used for the reduction of nausea and vomiting induced by cancer chemotherapy. Accumulated evidence suggests that the action of high-dose metoclopramide is related to the antagonism of 5-hydroxytryptamine-3 receptors (5-HT_3) at peripheral sites and possibly at central sites (*1,2*). BRL 43694[1] was developed recently as a selective 5-HT3 receptor antagonist. On the basis of a study in healthy volunteers, we initiated a pilot study of BRL 43694 in patients receiving strongly emetogenic cancer chemotherapy.[2]

From August 1987 to February 1988 we treated eight female and 12 male ambulatory tumor patients having a median age of 45 years (range, 24-65) with BRL 43694 administered as a 30-minute infusion 1 hour after the administration of the cytostatics. The first seven patients were treated with a dose of 40 μg/kg body weight. Thereafter, we increased the dose to 100 μg/kg. Thirteen patients received cisplatin $\geq$50 mg/m^2 as their first course of chemotherapy; seven patients were established vomiters (these patients had experienced >5 vomiting episodes during a previous course of chemotherapy despite conventional antiemetic treatment with a combination of high-dose metoclopramide, methylprednisolone, and flunitrazepam). All patients were hospitalized to receive their chemotherapy and antiemetic drugs. A research nurse recorded the number of vomiting episodes, the volume of emesis, and the duration of nausea, retching, and vomiting. The antiemetic effect was assessed semiquantitatively with the following scoring system as recorded during the previous hour: no nausea, retching, or vomiting = 0; nausea = 1; retching = 2; vomiting (single episode) = 3; and vomiting (multiple episodes) = 4. After each hour the patient was given a score, and the values for the 24-hour period were added together. The antiemetic efficacy was defined according to the 24-hour score as follows: complete response = 0; major partial response = 1-6; minor partial response = 7-12; and failure >12.

The results are summarized in table 1. Nine patients (45%) had no vomiting episode; four patients (20%) had 1-2 episodes; six patients (30%) had 3-5 episodes; and only one patient with anticipatory vomiting experienced 11 vomiting episodes over 24 hours following the administration of the chemotherapy. According to our assessment, 70% of the patients were completely or partially protected from nausea and vomiting. The efficacy was better in the group of chemotherapy-naive patients, with 85% of the patients experiencing protection. Sixty percent of the patients experienced moderate vomiting (1-5 episodes) 24-48 hours after chemotherapy, and 40% experienced vomiting 48-72 hours after the chemotherapy. There was no suggestion that the higher dose of BRL 43694 offered greater protection. Thirteen patients received a second course and seven patients a third course of BRL 43694 on subsequent courses of chemotherapy. The antiemetic efficacy was maintained. No consistent adverse events were attributable to BRL 43694.

BRL 43694 is one of several new 5-HT3 receptor antagonists currently undergoing clinical evaluation. Our results in 20 patients receiving highly emetogenic cancer chemotherapy suggest that BRL 43694 is a highly active antiemetic. We expect that without effective antiemetic treatment all of our patients would have experienced severe protracted nausea and vomiting. Overall, 70% derived significant benefit, and the

[1]Tentatively designated Granisetron pending approval.

[2]Data on file. Beecham Pharmaceuticals, Research Division, Harlow, England.

Table 1. Antiemetic activity of BRL 43694

	Total	No prior therapy	Prior therapy
Number of patients	20	13	7
Median score (range)	6 (0-31)	3 (0-15)	15 (0-31)
No. of patients (%) showing			
Complete response	8 (40)	6 (46)	2 (28)
Major partial response	2 (10)	2 (15)	0 (0)
Minor partial response	4 (20)	3 (24)	1 (14)
Failure	6 (30)	2 (15)	4 (58)
Median No. of vomiting episodes (range)	1 (0-11)	0 (0-5)	3 (0-11)
Median volume of emesis in mL (range)	15 (0-1180)	0 (0-410)	355 (0-1180)

success rate was even higher in chemotherapy-naive patients (85%). Furthermore, the antiemetic activity of BRL 43694 was maintained upon retreatment. Finally, the essential lack of adverse effects makes the drug a very attractive antiemetic. Randomized trials comparing BRL 43694 to standard antiemetic therapy (high-dose metoclopramide plus dexamethasone) in chemotherapy-naive patients are currently under way to establish the full potential of BRL 43694 as a novel antiemetic drug.

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References

1. ANONYMOUS. 5-HT_3 receptor antagonists: a new class of antiemetics. Lancet 1987;1: 1470-1471.
2. BOYLE EA, MINER WD, SANGER GJ. Antiemetic activity of BRL 43694, a novel 5-HT_3 receptor antagonist. Br J Cancer 1987;56:227.